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ANALGESICS, ALLERGY AND ASTHMA

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1 Recent studies of idiosyncratic reactions to analgesics have revealed several clinical patterns with a different pathogenesis.

2 In the pathogenesis of a common type of asthma precipitated by aspirin, inhibition of cyclo-oxygenase leading to disturbances in metabolism of arachidonic acid is of fundamental importance.

3 In some patients with urticaria/angioedema, symptoms are due to inhibition of cyclo-oxygenase by analgesics; in others the cause might be impurities in commercial preparations of aspirin; and in others the mechanisms are still unknown.

4 There is a distinct group of patients who develop anaphylactic shock or urticaria following administration of pyrazolone drugs, but who tolerate aspirin and other cyclo-oxygenase inhibitors. This type of hypersensitivity seems to have an immunological background.

Introduction

THE first idiosyncratic reactions to aspirin were recognized soon after its introduction, and a recent large survey (Irey, 1976) has listed aspirin among the ten drugs most frequently involved in adverse reactions. The majority of healthy people, however, tolerate aspirin and related anti-inflammatory drugs well. In some common diseases (for example asthma, urticaria), intolerance to aspirin-like drugs is frequent and constitutes a major clinical problem.

Aspirin-induced asthma

Definition and prevalence

In some patients with asthma, aspirin and other non-steroidal anti-inflammatory drugs precipitate asthmatic attacks. This is a distinct clinical syndrome, called aspirin-induced asthma.

The reported incidence of aspirin-induced asthma in adults varies according to the methods used. When oral challenge coupled with spirometry is performed the frequency among asthmatics is 8% to about 25%. Other surveys relying only on history have found a lower prevalence, for example, 4% (Szczeklik, 1980). Challenge tests have provided results which are more realistic than history alone, which is subject to the whims of memory.

It is generally assumed that aspirin-induced asthma is very uncommon in children. However, in two recent studies using oral challenge tests, the frequency has been reported as 28% (Rachelefsky, Carlson, Siegel & Steehm, 1975) and 13% Vedenthan, Menon, Bell & Bergin, 1977). In contrast, in another study none of 32 children with asthma, developed bronchoconstriction following aspirin ingestion (Schuhl & Pereyra, 1979).

Aspirin intolerance has been described in a few families. A familial predisposition, however, seems to be very rare. In our population of 500 patients with proved aspirin-induced asthma, we have found only two cases of familial intolerance.

Pathogenesis

Allergic mechanisms for aspirin-induced asthma have been excluded by numerous and extensive immunological studies. Furthermore, in aspirin-sensitive patients asthmatic attacks may be precipitated by several other analgesics with various chemical structures, which make immunological cross-reactivity most unlikely. Non-immunological concepts which still remain to be proven are: injury to kinin receptors by pre-existing disease which results in their paradoxical stimulation by aspirin, activation of the complement system by aspirin, slowly progressing acetylation of body proteins by aspirin and α-β-adrenergic imbalance. These and other concepts have been thoroughly and critically reviewed by Harnett, Spector & Farr (1978).

We put forward a hypothesis that in sensitive patients induction of the asthmatic attacks by aspirin-like drugs is due to inhibition of tissue prostaglandin biosynthesis (Szczeklik, Gryglewski & Czerniawska-Mysik, 1975a). The evidence in favour of this hypothesis is based on the finding that only cyclo-oxygenase inhibitors, that is, analgesics which suppress the generation of prostaglandins,

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thromboxane A_2 and prostacyclin *in vitro*, induce bronchoconstriction in sensitive patients (Szczeklik & Gryglewski, 1978). This conclusion stems from the results of an oral challenge test in which 21 different non-steroidal anti-inflammatory drugs were administered to 190 patients with aspirin-induced asthma (Szczeklik, Gryglewski & Czerniawska-Mysik, 1977; Serwońska, 1979).

Blockade of cyclo-oxygenase by aspirin-like drugs in sensitive patients can lead to adverse reactions through at least two simultaneously operating mechanisms. First, bronchi become deprived of the bronchodilator prostaglandin of the E type which, in turn, promotes the release of histamine. Indeed, prostaglandins of the E type are not only bronchodilators, but stabilize histamine stores in mastocytes. In aspirin-sensitive asthmatics, aspirin challenge results in a significant increase in plasma histamine (Stevenson, Arroyave, Bhat & Tan, 1976). Furthermore, aspirin-induced bronchoconstriction can be diminished or even prevented by drugs which either stabilize the mast-cell membranes (Basomba, Romar, Villamanzo & Campos, 1976) or block H_1-histamine receptors (Szczeklik & Serwońska, 1979). Second, inhibition of cyclo-oxygenase might lead to diversion of arachidonic acid metabolism towards lipoxygenase products, which in turn augment the release of histamine and anaphylactic mediators (Adcock, Garland, Moncada & Salmon, 1978). It is along these lipoxygenase pathways that novel compounds with conjugated trienes are formed, one being slow-reacting substance of anaphylaxis (SRS-A) (Borgeat & Samuelsson, 1979).

But why do cyclo-oxygenase inhibitors induce bronchoconstriction through the above mechanisms only in some but not in all asthmatics? We do not know. One explanation could be that aspirin-sensitive patients differ from other asthmatics as well as from healthy subjects by relying more on prostaglandin E bronchodilation than on β-adrenergic mechanisms (Szczeklik *et al.*, 1975a). Another possible explanation is that sensitivity of cyclo-oxygenase to aspirin in the bronchi of patients with aspirin-induced asthma becomes partly enhanced by a specific, but unknown infectious agent (Gryglewski, Szczeklik & Nizankowska, 1977). The possibility that in certain asthmatics an abnormal mechanism exists whereby aspirin might selectively block the release of the bronchodilator prostaglandin E_2 without also blocking the release of the bronchoconstrictor prostaglandin $F_{2\alpha}$ (Settipane, Chafee & Klein, 1974), seems unlikely (Patrono *et al.*, 1978).

Clinical symptoms, laboratory findings and diagnosis

The sequence of symptoms and the natural history of aspirin-induced asthma are so characteristic that based on extensive clinical observations, a typical or 'classic' case has been constructed (Samter & Beers, 1968). Beginning during the third or fourth decade of life, the typical patient starts to experience intense vasomotor rhinitis. Over a period of months chronic nasal congestion appears and physical examination reveals nasal polyps. Bronchial asthma and intolerance to aspirin develop during subsequent stages of the illness. The intolerance itself presents a unique picture: within minutes to hours following ingestion of aspirin, acute asthmatic attacks develop, often accompanied by rhinorrhea, conjunctival irritation and a scarlet flush of the head and neck. As many patients have taken aspirin in the past with impunity, the initial reaction is usually unexpected and, in fact, quite often not attributed to the drug. These reactions are dangerous. Indeed in highly sensitive patients shock may develop leading rapidly to death after ingestion of 1 tablet (300 mg) of aspirin.

Tartrazine, a yellow azo dye (FD&C No. 5) widely used for colouring foods, drinks, drugs and cosmetics, induces in some aspirin-sensitive subjects bronchoconstriction similar to that caused by aspirin and other cyclo-oxygenase inhibitors. About one half of the patients with positive aspirin challenge tests also have a positive tartrazine test as judged by the decrease in spirometric values (Stenius & Lemola, 1976). Samter & Beers (1968), however, have noticed that only 14 out of 182 patients intolerant to aspirin also reacted adversely to tartrazine. In a study with S. Bianco, P. Kamburoff and M. Serwońska (unpublished results), including patients from Italy, Poland and Switzerland, we have found tartrazine intolerance to be rare among patients with aspirin-induced asthma, affecting less than 10%. Unlike aspirin-like drugs, tartrazine does not inhibit cyclo-oxygenase activity in sheep seminal vesicles, guinea-pig lung microsomes, and human platelets (Gerber, Payne, Oelz, Nies & Oates, 1979). Very high concentrations of tartrazine are necessary to interfere with production of prostaglandins and thromboxanes in guinea-pig lungs perfused with arachidonic acid (Ceserani, Colombo, Robuschi & Bianco, 1978). It seems, therefore, that a cross-sensitivity between tartrazine and aspirin, observed sporadically in aspirin-sensitive asthmatics, is unlikely to be based on prostaglandin inhibition.

In aspirin-induced asthma, skin tests with common inhaled allergens are usually negative, and other signs of atopy are rarely present (Samter & Beers, 1968), but the blood eosinophil count is elevated. In contrast to Fisherman & Cohen (1974), we have been unable to detect any changes in template bleeding time following ingestion of aspirin 40 mg in 21 patients with aspirin-induced asthma compared with 17 normal subjects (Szczeklik, Musial & Serwońska, 1975). Our results are in agreement with both the clinical picture of aspirin-induced asthma in which haemorrhagic symptoms are absent, as well as with

the recent finding by Patrono *et al.* (1978) of unrelated susceptibility of platelet cyclo-oxygenase to inhibition by aspirin *in vitro*.

The definitive diagnosis of aspirin hypersensitivity can be made only with oral challenge tests. An interesting modification of the oral challenge tests was developed by Bianco, Robuschi & Petrigni (1977).

Prevention and therapy

Patients with aspirin-induced asthma should avoid aspirin and all products containing it. The number of such products is high; over 200 of them are currently on the United States market. Other drugs which are absolutely contradictated in patients with aspirin-induced asthma, because they precipitate bronchoconstriction, and lead to life-threatening attacks are: indomethacin, mefenamic, flufenamic and meclofenamic acids, ibuprofen, fenoprofen, ketoprofen, naproxen, diclofenac, amidopyrine, noramidopyrine, phenylbutazone, flumisole and ditazole. If necessary, patients with aspirin-induced asthma can safely take, even on a chronic basis, salicylamide, dextropropoxyphene, benzydamine and chloroquine (Nizankowska & Szczeklik, 1979). Paracetamol can also be taken with impunity by the majority of patients. It is, however, safer to give half a tablet first and observe for 2–3 h for symptoms. We have found such symptoms in 4 out of 79 patients with aspirin-induced asthma challenged with paracetamol. Similarly, phenacetin (which is metabolized to paracetamol) has precipitated bronchoconstriction in one out of 21 patients.

Unfortunately, avoidance of aspirin-like drugs does not stop the disease, which runs a chronic course. There is no specific therapy for this type of asthma. Disodium cromoglycate might help some patients, and we feel that a 2–3 week therapeutic trial is warranted in every patient with aspirin-induced asthma.

Asthma relieved by aspirin

A few patients with bronchial asthma have reported that aspirin decreases their shortness of breath. Although clinicians have been well aware of this phenomenon, the first reports appeared only recently (Kordansky, Adkinson, Norman & Rosenthal, 1978; Szczeklik *et al.*, 1978). Two such patients have been described in whom not only aspirin but several other analgesics produced striking relief of airway obstruction as evidenced by spirometric and plethysmographic studies.

With Eva Nizankowska we have studied five such patients, aged 21–62 years. In all, airway obstruction has been markedly reduced by aspirin and other cyclo-oxygenase inhibitors, that is, indomethacin, mefenamic acid and fenoprofen, but not by salicylamide and benzydamine, which do not inhibit prostaglandin biosynthesis. It was therefore logical to assume that the pharmacological removal of a product of arachidonic acid cyclo-oxygenation from the respiratory tract helps to overcome airway obstruction. Perhaps this product is a bronchoconstrictor, prostaglandin $F_{2\alpha}$, thromboxane A_2 or other as yet unknown metabolites.

Urticaria and angioedema

Intolerance to aspirin

A few individuals react to aspirin by developing urticarial wheals and angioneurotic oedema. However, many patients with chronic urticaria of various aetiology develop an obvious increase after taking aspirin. These two groups can be separated, as in the latter aspirin causes an exacerbation of urticaria only while the chronic urticaria is active, but does not induce eruptions during symptomless periods. It seems that 20–40% of patients with chronic urticaria have exacerbation of urticaria on ingesting aspirin (Warin & Smith, 1976). High salicylate concentrations have been found in the blood of patients with chronic urticaria (Noid, Schulze & Winkelmann, 1974).

It seems clear that all patients with urticaria should avoid aspirin in any form. Care should be also taken to exclude from the diet food-and-drug additives and colourants (for example, benzoates and tartrazine) to which some patients are intolerant (Juhlin, Michaëlsson & Zetterström, 1972). Recent surveys have reported intolerance to tartrazine in 8% of patients with chronic urticaria (Settipane *et al.*, 1976).

There is a clearly distinguishable subgroup of patients who link their cutaneous reactions to aspirin ingestion, and inhibition of prostaglandin synthesis seems to play an important role in pathogenesis (Szczeklik *et al.*, 1977). We call this type B hypersensitivity to prostaglandin inhibitors as opposed to type A (aspirin-induced asthma). The same aspirin-like drugs that induce bronchoconstriction in type A patients also produce angioedema associated with urticaria or rhinitis in type B patients. All the drugs causing positive reactions in both groups A and B are inhibitors of prostaglandin biosynthesis (due to blockade of cyclo-oxygenase), indomethacin being the most active in this respect. It is therefore not surprising that of several different drugs studied by Doeglas (1975), indomethacin most frequently induced cutaneous reactions in patients with urticaria and hypersensitivity.

Impurities contaminating commercial aspirin could be responsible for urticaria and angioedema in some patients (De Weck, 1971). These contaminants include acetylsalicylic anhydride, acetylsalicylic-salicylic acid and *cis*-disalicylate. Impurities present only in some commercial preparations of aspirin could explain why certain patients who give a clear history of aspirin-induced urticaria and angioedema show no reaction when re-challenged with aspirin (Szczeklik *et al.*, 1977).

Hypersensitivity to pyrazolone drugs

There is a group of patients who are hypersensitive to pyrazolone analgesics, but not to aspirin-like drugs (Szczeklik *et al.*, 1977). These patients, more often than those with hypersensitivity to prostaglandin inhibitors, have a family history of allergic diseases and a positive skin test to common allergens. Their serum IgE levels are also often elevated. Untoward reactions to pyrazolone analgesics can be very dangerous. Of 28 such patients 22 developed anaphylactic shock after taking a single dose of aminophenazone or noramidopyrine, whereas in the remaining six, urticaria/angioedema occurred (Czerniawska-Mysik & Szczeklik, 1980). Scarification and/or intracutaneous tests carried out with aminophenazone or noramidopyrine 2–12 months after the acute reaction were positive in all patients. On the other hand, oral challenge tests with therapeutic doses of aspirin, indomethacin, fenamates and paracetamol were all negative.

Hypersensitivity in lupus erythematosus

Hypersensitivity reactions to drugs are frequently observed in patients with systemic lupus erythematosus. It is becoming evident that non-steroidal anti-inflammatory drugs are no exception to this rule.

We have found reports on eight patients with systemic lupus erythematosus who developed adverse reactions to ibuprofen (Mandell, Shen & Hepburn, 1976; Szczeklik *et al.*, 1977; Sonnenblick & Abraham, 1978). These reactions were characterized by sudden appearance of high fever, abdominal pain and rash. Serum transaminases concentrations were increased in some patients. Increased concentrations of serum transaminases also seem to be common in patients with active systemic lupus erythematosus, who are receiving aspirin (Seaman, Ishak & Plotz, 1974). The hepatotoxic effect of aspirin in these patients may not be due to allergic reaction but to a disturbance in aspirin transformation resulting in the formation of a toxic metabolite (Anonym, 1974).

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Discussion

PROFESSOR MANNAIONI asked if Professor Szczeklik had any direct evidence that classical prostaglandins protect mast cells from histamine release or whether the new prostaglandins were histamine releasers? In his hands prostaglandins of the E and I series were completely ineffective as far as histamine release was concerned in isolated, purified rat mast cells.

PROFESSOR SZCZEKLIK replied that he had not done any studies on the prevention of histamine release by animal mast cells. However, there had been reports that prostaglandins of the E series protected isolated mast cells from the release of histamine and other mediators.

Following aspirin challenge in patients with aspirin-induced asthma, histamine levels greatly increased and were parallel with the action of the drug. This did not occur in other asthmatics given aspirin who were not hypersensitive to the drug.

He said thromboxane A_2 was now generally believed to be one of the bronchoconstrictors which was released during several allergic reactions, but prostacyclin probably has little to do with the maintenance of bronchial tone. When he gave prostacyclin by inhalation to about 30 patients with asthma, there was no effect on pulmonary function studies.